TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Higgins and Kjelsberg, 1967, U.S.A. (*83*).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.	*Males* / *Females* NS ..... 209.9 (360) / 210.1 (1,439) Cigarette ..... 212.5 (1,426) / 212.4 (910)	
Pincherly and Wright, 1967, England (*150*).	2,000 men participating in executive health examinations 28–70 years of age.	*Serum cholesterol mg. percent* / *Percentage with serum cholesterol >270 mg. percent* NS (677) ..... 236.2 / 19.0 Ex-smoker (388) ..... 246.0 / 28.0 1–19 cigarettes/day (424) ..... 239.2 / 24.0 >20 cigarettes/day (511) ..... 249.4 / 30.0	The authors noted that smokers showed significantly higher ($p<0.001$) serum cholesterol levels than nonsmokers.
Van Buchem, 1967, Netherlands (*199*).	918 randomly chosen males 40–59 years of age for entry into prospective study.	*Serum cholesterol* *0–209 mg. percent* / *210–249 mg. percent* / *>250 mg. percent* NS ..... 12.4 (32) / 14.0 (44) / 14.2 (41) Cigarette SM ..... 71.6 (184) / 67.8 (213) / 68.2 (197) Other ..... 16.0 (41) / 18.2 (57) / 17.6 (51)	The authors found no correlation between smoking and serum cholesterol levels.
Boyle et al., 1968, U.S.A. (*28*).	1,104 male factory employees 20–64 years of age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS ..... 243 (519) / 0.325 SM ..... 251 (576) / 0.351 $p<0.005$ / $p<0.001$	Beta-lipoproteins were found to increase with age, but smokers had higher levels than nonsmokers at all ages.
Caganova et al., 1968, Czechoslovakia (*36*).	49 males living in youth hostel, 21.6 average age.	*Serum cholesterol mg. percent* / *Serum Beta-lipoprotein mg. percent* NS (34) ..... 188.20 / 359.80 SM (15) ..... 214.20 / 498.40 $p<0.025$ / $p<0.001$ *Beta/alpha lipoprotein ratio* NS (34) ..... 1.16 SM (15) ..... 1.55 $p<0.025$	

TABLE A7.—*Differences in serum lipids between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Modzelewski and Malec, 1969, Poland (*133*).	140 males 20–68 years of age.	*Serum-cholesterol*: NS (20) $p<0.01$ Heavy smokers *Serum Beta-lipoproteins*: NS $p<0.01$ Heavy smokers *Serum free fatty acids*: NS $p<0.01$ Heavy smokers	
Kjeldsen, 1969, Denmark (*113*).	934 employees of various firms in Copenhagen.	*Serum cholesterol mg. percent* NS (196) ..... 236 SM (738) ..... 247 $p<0.01$	
Pozner and Billimoria, 1970, England (*151*).	64 male and female healthy volunteers 19–30 years of age.	*Serum cholesterol mg. percent* / *Serum triglycerides mg. percent* / *Total phospholipids mg. percent* NS(20) ..... 176.3 / 68.6 / 193.4 Light SM(17) ..... 172.1 / 68.4 / 188.9 (Over 7.3 cigarettes/day) Heavy SM(27) ..... 200.0 $p<0.05$ / 87.6 $p>0.05$ / 215.0 $p<0.001$ (Over 22.5 cigarettes/day)	Significant figures refer to heavy smokers as compared with nonsmokers.

[1] Unless otherwise specified, disparities between the total number of cases and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE A8.—*Blood pressure differences between smokers and nonsmokers*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results				Comments
Dawber et al., 1959, U.S.A. (47).	1,253 male and female residents of Framingham.		*Systolic blood pressure*			No association found between systolic blood pressure and smoking.
			Ages 29–44		*45–59*	
		NS (149)	138.8		143.0	
		Cigarettes (874)	132.5		140.3	
		<10 (75)	134.7		144.0	
		10–19 (134)	129.4		141.6	
		20–39 (551)	132.2		138.9	
		>40 (114)	136.1		141.5	
		Pipe and cigar (128)	135.0		141.9	
Edwards et al., 1959, England (56).	1,737 male patients of general practitioners over 60 years of age.		*Proportion of males with "Hypertension" (≧200/≧100 mm. Hg.)*			
		NS	27.2 percent (151)			
		Cigarettes	20.5 percent (780)			
		Pipe	25.9 percent (341)			
Karvonen et al., 1959, Finland (97).	525 males in various regions of Finland 20–59 years of age.		*Systolic blood pressure*			No data on pipe and cigar smokers. No statistical significance noted.
			West Finland	*East Finland*	*Helsinki*	
		NS	139.2 (64)	142.6 (39)	132.8 (62)	
		SM	133.2 (91)	135.4 (103)	129.8 (166)	
			Diastolic blood pressure			
		NS	84.7	86.8	89.6	
		SM	81.9	84.1	86.8	
Clark et al., 1967, U.S.A. (43).	1,859 male civil servants.		*Mean systolic blood-pressure*		*Mean diastolic blood-pressure*	Nonsmoker and smoker groups were of similar average age.
		NS (728)	137.0		83.9	
		SM (407)	133.6	($p \leqq 0.05$)	82.5	($p \leqq 0.05$)

TABLE A8.—*Blood pressure differences between smokers and nonsmokers (cont.)*

(Actual number of individuals shown in parentheses)[1]

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Results	Comments
Higgins and Kielsburg, 1967, U.S.A. (*83*).	5,030 male and female residents of Tecumseh, Michigan, 16–79 years of age.	*Age adjusted mean systolic blood pressure*: *Males* / *Females*; *Age adjusted mean diastolic blood pressure*: *Males* / *Females* NS ..... 137.9 (360) / 84.5 (1439); 136.6 (360) / 82.1 (1439) Cigarette ... 136.4 (1426) / 81.4 (910); 131.6 (1426) / 79.0 (910) ($p<0.001$)	
Reid et al., 1967, England (*155*).	676 male British and 625 male American postal workers 40–59 years of age.	*Mean systolic blood pressure (adjusted for difference in weight)*: *UK* / *U.S.A.*; *Mean diastolic blood pressure*: *UK* / *U.S.A.* NS ..... 128.2 (45) / 124.8 (89); 79.3 / 81.0 1–14 grams 130.2 (27) / 133.0 (60); 79.4 / 82.1 15–24 grams 128.5 (232) / 127.7 (169); 78.5 / 77.3 >25 grams 127.9 (70) / 128.1 (218); 77.5 / 77.1 All amounts 129.1 (519) / 128.6 (447); 78.7 / 77.8	The author did note SM-NS blood pressure differences prior to controlling for weight, but not after such control.
Tibblin, 1967, Sweden (*187*).	895 males in Göteborg, Sweden, born in 1913.	*Blood pressure* ≦*110*/≦*70* (*89*); *115–145/75–95* (*468*); *150–170/100–110* (*220*); >*175*/>*115* (*75*) NS ..... 18.0; 23.0; 25.5; 34.7 1–14 cigarettes ..... 29.2; 29.2; 25.5; 18.7 >15 cigarettes ..... 28.1; 20.9; 15.5; 17.3 Pipe and cigar 11.2; 8.6; 10.0; 4.0	Numbers in parentheses represent total in blood pressure group. The author noted a stepwise decrease with level of blood pressure as smoking increased.

[1] Unless otherwise specified, disparities between the total number of individuals and the sum of the individual smoking categories are due to the exclusion of either occasional, miscellaneous, mixed, or ex-smokers.

TABLE A17.—*Incidence of new coronary heart disease by smoking category and behavior type for men 39–49 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Never smoked	Smoking group					
		Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1–15	16–25	26 and over	
A	[1]5.3(5)	13.8 (7)	1.3(1)	1.6(1)	15.8(15)	14.9(16)	9.3(45)
B	1.3(2)	5.1 (3)	2.2(2)	7.3(4)	3.1 (3)	4.9 (4)	3.3(18)
Total	2.9(7)	9.1(10)	1.8(3)	4.9(5)	9.3(18)	10.4(20)	6.2(63)

Source	Analysis of variance table				
	Sum of squares	d.f.	Mean square	F	P
Within cells	59.471	2,245	0.026	..	..
Regression on age	0.458	1	0.458	17.296	0.001
Between smoking groups [2]	0.504	5	0.101	3.81	0.002
Between behavior types [2]	0.329	1	0.329	12.43	0.001
Interaction	0.396	5	0.079	2.99	0.011

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

SOURCE: Jenkins, C. D. et al. (*90*).

TABLE A18.—*Incidence of new coronary heart disease by smoking category and behavior type for men 50–59 years of age*

(Numbers in parentheses are number of CHD cases in each subgroup)

Behavior type	Smoking group						
	Never smoked	Former cigarette smokers	Current and former pipe and cigar only	Cigarettes			Total
				1-15	16-25	26 and over	
A	[1]12.4(5)	18.6(8)	21.8 (8)	16.4(5)	21.5 (9)	30.0(14)	20.4(49)
B	10.0(4)	5.1(1)	8.4 (3)	4.7(1)	21.1 (7)	19.1 (5)	12.0(21)
Total	11.1(9)	14.2(9)	14.9(11)	11.5(6)	21.3(16)	26.0(19)	16.8(70)

Source	Analysis of variance table				
	Sum of squares	d.f.	Mean square	F	P
Within cells	63.527	911	0.070	..	..
Regression on age	0.177	1	0.177	2.54	0.111
Between smoking groups [2]	0.522	5	0.104	1.496	0.188
Between behavior types [2]	0.296	1	0.296	4.24	0.040
Interaction	0.129	5	0.026	0.37	0.870

[1] Rates are age-adjusted annual incidence per 1,000 men.

[2] Mean squares for "between smoking groups" and "between behavior types" are each computed eliminating the general mean and the other main effect but ignoring interaction, thus yielding an estimate of each main effect unconfounded by other significant main effects.

SOURCE: Jenkins, C. D. et al. (*90*).

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Bellet et al., 1941, U.S.A. (*21*).	39 experiments on dogs which had undergone coronary artery ligation up to 45 days before.	Inhalation of tobacco smoke in chamber.	Definite increase.	Definite increase.			Coronary artery ligation increased the frequency of nicotine-induced severe arrhythmias; these became less evident with increasing time since ligation.
		Nicotine intravenous 0.2-1.2 mg./kg.	Definite increase.	Definite increase.			
Burn and Rand, 1958, England (*35*).	10 rabbits, 5 experimental, 5 control, isolated atria.	Experimental animals pretreated with intraperitoneal nicotine and the atria of both groups excised and perfused with nicotine.					Isolated atrial specimen showed increased rate and increased amplitude of contractions with administration of nicotine proportional to pretreatment. These reactions were blocked by reserpine, and the authors consider nicotine effects to be mediated by catecholamine release from chromaffin store in myocardium.
West et al., 1958, U.S.A. (*208*).	33 normal adult mongrel dogs.	Coronary intra-arterial nicotine: I. 0.2–2.2 μg./kg. II. 0.04–1 μg./kg.	Definite increase (systolic).				I. Myocardial contractility increased 40–90 percent in 15/15 animals tested accompanied by ST segment depression and T-wave inversion and blocked by tetraethylammonium chloride. II. Coronary blood flow increased 19 percent upon left circumflex artery injection; coronary blood flow showed no change upon left anterior descending artery injection, 64 observations on 10 dogs. (Tetraethylammonium chloride blocked CBF increase.) The authors found no evidence of coronary vasoconstriction in these healthy animals.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Cardiac output	Coronary blood flow	Comments
Forte et al., 1960, U.S.A. (*65*).	27 observations on 8 dogs.	Intravenous nicotine up to 21.5 mg. given as 5–15 μg./kg./minute.		Definite initial increase then decrease.		No change.	No significant change in either left ventricular work or myocardial oxygen extraction.
Kien and Sherrod, 1960, U.S.A. (*112*).	21 adult dogs	Cigarette smoke under positive pressure via tracheostomy. Nicotine 20 μg./kg. intravenously. Epinephrine 5 μg./kg. intravenously.		Definite increase.	Definite increase.	Increase following increase in blood pressure and cardiac output.	Effects of cigarette smoke were duplicated by intravenous nicotine and epinephrine. During cigarette smoke inhalation, it was noted that without blood pressure or output changes, coronary blood flow did not increase and that while adverse EKG changes were noted they correlated more closely with decreased cardiac oxygen utilization than with actual cardiac work.
Travell et al., 1960, U.S.A. (*189*).	14 normal rabbits and 16 rabbits with severe cholesterol-induced atherosclerosis.	Intravenous nicotine 0.01–0.1 mg.				Definite increase in normals.	Nicotine-induced coronary blood flow and heart rate increase in the atherosclerotic animals required 10 times and 2 times, respectively, the amounts required in the normal animals.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, coutry, reference	Number and type of population	Smoking procedure			Comments
Bellet et al., 1962, U.S.A. (*22*).	I. 10 normal dogs II. 9 dogs at varying intervals following coronary artery ligation. III. 7 dogs with varying grades of artificially-induced coronary artery narrowing.	Intravenous nicotine, 20 μg./kg./minute for 15–20 minutes.		I. 125 percent increase II. 82.5 percent increase III. 83.3 percent increase	The authors noted that: 1. The response of coronary blood flow to nicotine resembled that of anoxemia in the presence of coronary insufficiency. 2. The greater the induced coronary impairment the smaller the increment in coronary blood flow.
Leaders and Long. 1962, U.S.A. (*125*).	15 adult mongrel dogs.	Left anterior descending intracoronary injection of nicotine or norepinephrine.			Nicotine and norepinephrine both increased coronary vascular resistance and myocardial contractile force (the former measured by a constant-volume variable-pressure system). The action of nicotine was blocked by pretreatment with hexamethonium, pentolinium, reserpine, or guanethidine.
Larson et al., 1965, U.S.A. (*124*).	13 adult mongrel dogs.	Intravenous nicotine, 0.02 mg./kg./minute for 10–12 minutes.	Definite increase.	Definite increase.	Systemic vascular resistance and pulmonary artery and left atrial pressures showed biphasic responses of increase followed by decrease.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Folle et al., 1966, U.S.A. (*64*).	7 dogs of 30 investigated (Remainder experienced catheterization failures).	I. Cigarette smoke inhalation to isolated left lower lobe and then blood perfused coronary arteries. II. Cigarette smoke to rest of lung and then blood passed to general circulation. III. Nicotine perfused directly into left coronary artery.	I. No change in coronary vascular resistance. II. 5/6 showed increase in coronary vascular resistance due, according to the author, to general sympathetic nervous system stimulation. III. 4/5 showed increase in coronary vascular resistance. The authors conclude that the cardiac effects of tobacco arise almost entirely from the extracardiac actions of smoking instead of the direct response of the heart.
Nadeau and James, 1967, U.S.A. (*142*).	26 dogs	Nicotine 0.01–10.0 μg. into sinus node artery.	Heart rate showed initial slowing (due probably to vagal stimulation) followed by acceleration (due probably to vagal paralysis and catecholamine release). No systemic blood pressure changes noted.
Romero and Talesnik, 1967, U.S.A. (*156*).	16 experiments on isolated cat heart.	Nicotine in varying doses in perfusate of coronary arteries.	Over 5 μg. of nicotine was found to produce an initial bradycardia associated with increased coronary flow, followed by prolonged tachycardia with an initial decrease in coronary blood flow followed by a prolonged increase. Pretreatment with hexamethonium or reserpine prevented both the myocardial stimulation and the increase in coronary blood flow. The authors consider the action of nicotine to be a combination of a direct vasoconstrictive effect and an indirect catecholamine-releasing vasodilating effect.
Puri et al., 1968, U.S.A. (*152*).	22 mongrel dogs	I. (14) Intravenous nicotine 50 μg./kg./minute for 3–4 minutes II. (8) Propranolol pretreatment, then 50 μg./kg./minute nicotine for 3–4 minutes	I. Nicotine produced a definite increase in the force and velocity of left ventricular contraction. II. Pretreatment with propranolol produced (relative to results of Group I): (a) A further increase in left ventricular systolic pressure. (b) A decrease in velocity of shortening. (c) A significant increase in left ventricular end-diastolic pressure. The authors conclude that propranolol probably impairs the norepinephrine-like effects of nicotine on the myocardium while enhancing its peripheral vasopressor effects.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Balazs et al., 1969, U.S.A. (*16*).	Beagle dogs with lesions induced in myocardium by either: (1) Isoproterenol pretreatment, or (2) ligation of the anterior descending coronary artery.	I. Normals (3–6 per experiment): (a) 4 μg./kg. intravenous nicotine, (b) 40 μg./kg. intravenous nicotine. II. Experimental (3), 4 μg./kg. intravenous nicotine	I. (a) No evidence of arrhythmias; (b) A single or a few ectopic beats in 2/3 normal dogs. II. Extrasystoles noted in 2/3 animals during the first day after cessation of the arrhythmia induced by the lesion alone, but not thereafter. These and nicotine-induced arrhythmias were of a short duration.
Greenspan et al., 1969, U.S.A. (*74*).	Cardiac muscle isolated from the right ventricle of 10 adult dogs.	Nicotine 2–100 μg./cc. in Tyrode's solution perfusate.	Nicotine perfusion produced: (1) An increase in myocardial contractile force apparently independent of adrenergic innervation. (2) An increased automaticity of the Purkinje fiber system apparently due to release of catecholamines from chromaffin tissue stores. (3) A decrease in conduction velocity. The authors conclude that the latter two effects probably predispose to arrhythmia formation.
Saphir and Rapaport, 1969, U.S.A. (*166*).	88 mongrel cats	Nicotine 5–12 μg./kg. injected intraarterially to mesenteric circulation.	I. Mesenteric injection of nicotine was followed with 1–2 seconds by: (a) Increased left ventricular systolic pressure (LVSP). (b) Increased systemic resistance. (c) Enhanced myocardial performance. II. Left ventricular injection of nicotine was followed by: (a) Increased LVSP. (b) Bradycardia. (c) Enhanced myocardial performance greater than that seen in mesenteric-injected group. III. Pretreatment with phenoxybenzamine diminished the increase in LVSP while propranolol pretreatment diminished the enhancement of myocardial performance while LVSP still showed a significant increase. IV. Mesenteric sympathetic nerve section led to a diminished response. The authors conclude that the cardiovascular responses to nicotine may be neurogenic in nature with receptors distributed in certain abdominal arteries.

TABLE A20.—*Experiments concerning the effects of smoking and nicotine on animal cardiovascular function (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Comments
Leb et al., 1970, U.S.A. (*126*).	12 mongrel dogs and CBF measured with use of Rb^{34} and digital counter.	Nicotine 100 μg./kg. for 2 minute intravenously.	Effective Coronary Flow (ECF) is that part of the total coronary flow (TCF) which is "effectively" involved in nutrient exchange. Nicotine injection was followed by: (1) 96.6 percent increase in TCF. (2) 51.1 percent increase in ECF. (3) 73.1 percent increase in myocardial oxygen consumption and analysis revealed that capillary flow increased almost proportionately to myocardial oxygen consumption whereas the increase in TCF was far in excess. (4) Definite increases in cardiac output, heart rate, left ventricular work, and aortic pressure.
Ross and Blesa, 1970, U.S.A. (*160*).	10 dogs undergoing instantaneous coronary arterial flow measurement.	Nicotine 10–100 μg. intracoronary injection.	Nicotine injection was followed by: (1) Increased contractile force. (2) Decreased myocardial contraction time. (3) Decreased time necessary to reach peak tension. (4) Decreased total stroke systolic CBF. (5) Increased total stroke diastolic CBF. (6) Increased total stroke CBF. (7) Changes similar to intraarterial epinephrine. (8) Changes blocked by pentolinium pretreatment. (9) No change in heart rate or blood pressure. The authors conclude that catecholamines released from the ventricular myocardium mediated these responses to nicotine.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Russek et al., 1955, U.S.A. (*164*).	I. 28 healthy male smokers 21–60 years of age (average 42). II. 37 male patients with overt clinical CHD 42–70 years of age (average 54), 6 were nonsmokers.	1 standard and 1 denicotinized cigarette.	I. Increase. II. Increase.	Increase. Increase.	EKG: I. 16/28 showed significant changes. II. No significant changes. BCG: I. . . . II. 18/37 showed significant change.				Denicotinized cigarettes evoked changes of a lesser degree in normals and CHD subjects, but in the latter group there was no significant difference between these changes.
Bargeron et al., 1957, U.S.A. (*17*).	14 of 30 healthy adult male volunteer smokers and nonsmokers who underwent successful catheterization 18–53 years of age.	1 cigarette inhaled at intervals of 20 seconds.	Insignificant increase.	Increase.				Definite increase.	Coronary vascular resistance fell significantly. Myocardial 0_2 usage underwent no significant change. Pyruvate extraction fell slightly. Authors consider lack of increase in heart rate as due to baseline apprehensive tachycardia.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Regan et al., 1960, U.S.A. (*154*).	7 males with history of EKG-proven myocardial infarction undergoing cardiac catheterization.	2 standard cigarettes in 25 minutes inhaled at minute intervals.	Definite increase.	Definite increase.			Increase.	No significant change.	Myocardial 0_2 consumption rose slightly in 3 out of 7. The author considers that the EKG changes noted on smoking are probably due less to decreased coronary blood flow than to increased workload (oxygen need) where oxygen supply does not increase. Noted no evidence of myocardial ischemia during smoking.
Thomas and Murphy, 1960, U.S.A. (*186*).	113 clinically healthy young males.	One standard cigarette smoked at own pace.	Definite increase.	Definite increase.		Definite increase.	Definite increase.		Pulse pressure showed a decrease. Smokers responded slightly but significantly more actively than nonsmokers. BCG changes were increasingly common with increasing age, weight, and serum cholesterol.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Von Ahn, 1960, Sweden (*202*).	The author reviews a series of experiments performed between 1944–1954.	Cigarette smoking.	Increase.		EKG: Slight ST segment depression and T-wave flattening.				EKG changes more prominent in young, clinically healthy subjects than in older, habitual smokers. Intravenous nicotine and smoking showed identical cardiovascular effects. Smoking elicited angina pectoris in a number of CHD patients.
Irving and Yamamoto, 1963, England (*89*).	5 normal males, 15 patients with diseases not defined, 19–66 years of age, all moderate-heavy cigarette smokers.	(a) Sham smoking.	(a) No change.	No change.		(a) No change.	No change.		Cardiac output measured by dye dilution technique.
		(b) Non-inhalation smoking.	(b) No change.	No change.		(b) No change.	No change.		
		(c) 2 standard cigarettes in 10 minutes.	(c) Definite increase.	Widened pulse, pressure.		(c) Definite increase.	Definite increase.		
		(d) Nicotine 0.6 mg. intravenously.	(d) Definite increase.	Definite increase.		(d) Definite increase.	Definite change.		

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Penteost and Shilling-ford, 1964, U.S.A. (129).	I. 14 volunteers with clinical CHD, 13/14 smokers, average age 39.5.	Single cigarette smoked at own rate in 6–7 minutes.	Definite increase in all groups.	Definite increase in all groups.		I. 10 percent increase.	27 percent increase.		
	II. 5 patients with angina pectoris, all smokers, average age 43.4.					II. Intermediate change.	Intermediate change.		
	III. 14 patients with history of definite myocardial infarction, all smokers average age 54.1.					III. 8 percent decrease.	1 percent increase.		
Frankl et al., 1965, U.S.A. (62)	5 male and 3 female patients with healed myocardial infarction 48–69 years of age 2/8 nonsmokers.	2 standard cigarettes in 10 minutes at rest and under graded exercise.	Definite increase at rest and at exercise.			No significant changes at rest or during exercise.	No significant changes at rest or during exercise.		The author contrasts this response with that seen among healthy young individuals.

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Sen Gupta and Ghosh, 1967, India (*171*).	6 healthy male nonsmokers. 8 healthy male smokers. 6 patients with CHD, nonsmokers. 5 patients with CHD, smokers. 36–64 years of age.	1 untipped cigarette in 5–7 minutes.	Increase in all groups.	Increase in all groups.	No change. 6/8 showed ST changes. All showed ST and T-wave changes. All showed ST and T-wave changes.				
Aronow et al., 1968, U.S.A. (*5*).	10 male patients with classical angina pectoris. 32–59 years of age	1 standard high nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					Product of systolic blood pressure and heart rate showed a significant increase on smoking while left ventricular ejection time values did not. All patients developed angina more rapidly under a constant exercise load if they had smoked before exercising.
Kerrigan et al., 1968, U.S.A. (*102*).	24 male and 1 female healthy smokers, average age, 45. 8 male and 2 female healthy nonsmokers, average age 33.	2 filtered cigarettes in 15 minutes with measures taken at rest and during exercise.	Definite increase under rest and exercise conditions.	Definite increase under rest and exercise conditions.			Cardiac index. Definite increase under rest and exercise conditions.		The increase in cardiac index, heart rate, and blood pressure during exercise with smoking was the sum of such increases seen with smoking or exercise separately. Neither group showed increases in peripheral vascular resistance.

TABLE A21.—*Experiments concerning the effects of smoking and nicotine on the cardiovascular system of humans (cont.)*

Author, year, country, reference	Number and type of population	Smoking procedure	Heart rate	Blood pressure	Electrocardiogram ballistocardiogram	Stroke volume	Cardiac output	Coronary blood flow	Comments
Allison and Roth, 1969, U.S A. (*3*).	30 healthy male subjects. 19–59 years of age.	2 standard cigarettes smoked in 12–16 minute period.	Definite increase.	Increase.			Increase followed by decrease within 20 minutes.		Definite decrease in pulmonary blood volume as indicated by impedance methods of thoracic pulse volume.
Aronow and Swanson, 1969, U.S.A. (*7*).	10 male patients with classical angina pectoris. 32–59 years of age.	1 low nicotine cigarette in 5 minutes.	Definite increase.	Definite increase.					All patients developed angina sooner if they smoked before exercising.
Aronow and Swanson, 1969, U.S.A. (*6*).	10 male patients with classical angina pectoris. 32–59 years of age.	1 non-nicotine cigarette in 5 minutes.	No change.	No change.					No difference noted in time or onset of exercise-induced angina between smoking and non-smoking procedures.
Marshall et al., 1969, U.S.A. (*129*).	42 normotensive healthy male prisoners 18–50 years of age. 13 nonsmokers. 16 moderate smokers. 13 heavy smokers.	3/4 of one standard cigarette.	Insignificant increase.	Insignificant increase.					Blood pressure response to cold pressor test noted to be greater in heavy smokers. Presyncopal reactions to 40 degree head-up tilt more frequent in smokers.

TABLE A22.—*Experiments concerning the effect of nicotine or smoking on catecholamine levels*

Author, year, country, reference	Number and type of subject	Procedure	Results
Watts, 1960, U.S.A. (*208*).	11 dogs	0.02–0.60 mg/kg. nicotine intravenously.	Nicotine administration was associated with significant increases in peripheral arterial epinephrine levels. Ganglionic blocking agents prevented this effect.
Westfall and Watts, 1963, U.S.A. (*210*).	22 mongrel dogs	Cigarette smoking via tracheal cannula; 1 cigarette/8 minutes for 35 minutes.	Regular cigarette smoke evoked a statistically significant increase in adrenal vein, vena cava, and femoral artery levels of epinephrine. Cornsilk cigarette smoke evoked no change.
Westfall and Watts, 1964, U.S.A. (*211*).	21 male volunteers approximately 25 years of age; 11 nonsmokers, 10 smokers.	3 cigarettes smoked in 30 minutes.	Smoking at rate noted for 2½ hours evoked a significant increase in urinary epinephrine, but not norepinephrine levels.
Westfall et al., 1966, U.S.A. (*209*).	Mongrrel dogs	Standard cigarette smoke exposure via endotracheal tube. Smoke inhalation every third inspiration for 3 minutes.	Smoke inhalation evoked a rise in cardiac output, stroke volume, blood pressure, and plasma catecholamine levels. Pretreatment with propranolol diminished the cardiac output and stroke volume responses but increased the blood pressure response—the latter effect due to the release of alpha-receptor activity by beta-blockade.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration*

Author, year, country, reference	Number and type of animal	Procedure	Results
Adler et al., 1906, U.S.A. (*2*).	Rabbits	Nicotine 1.5 mg. intravenously in 5 percent solution 6 of 7 days per week for more than 4 months.	The authors noted an arterionecrosis of the aorta, affecting mainly the inner muscular layers. Macroscopically, early changes consisted of small areas of calcareous ridging and aneurysmal dilatation without notable fatty degeneration or intimal discontinuity. Microscopically, early changes appeared in the muscle cells of the media, and "chalky" deposits were noted between the elastic fibers.
Hueper, 1943, U.S.A. (*86*).	I. 6 mongrel dogs.	Nicotine subcutaneously. Increasing dosage up up to 2.5 cc. of 3 percent solution for 1 month.	I. 4/6 animals died of infection and showed marked edema and focal hyalinization of the media of the aorta and large elastic arteries. 2/6 animals were sacrificed and showed thickening and hyalinization of the walls of the coronary arteries and edema of the media as well as endothelial proliferation of other arteries.
	II. 60 rats.	Increasing doses up to 1 cc. of 1 percent solution for 1 month.	II. Much less aortic involvement than that found in the dogs; infrequent arteriolar changes consisting of fibrosis and thickening of the media.
Maslova, 1956, USSR (*130*).	Rabbits	I. (10) Nicotine subcutaneously 1 percent solution 0.2 cc. daily for 115 days.	I. Aortic wall—acute swelling of elastic fibers with focal fragmentation and partial disintegration—no intimal fat deposits seen. Coronary vessels—thickening of the vessel wall—no fat deposits.
		II. (14) Nicotine plus 0.2 grams cholesterol per day.	II. Aorta—"massive" deposits of "cholesterol" in the intima and vasa vasorum with "loosening" of the aortic wall. Coronary vessels—the larger vessels showed moderate fat deposition and the smaller vessels showed swelling of the elastica.
		III. (10) Cholesterol only.	III. Aorta—isolated lipid deposition in the arch and ascending portions only. Coronary vessels—no fat deposition.
Czochra-Lysanowicz et al., 1959, U.S.A. (*46*).	Rabbits	I. (10) 1.0 g. cholesterol/day for 100 days.	Index of aortic lesion density (cholesterol infiltration):
		II. (10) Cholesterol plus 0.0015 g. nicotine/day intravenously.	I. 2.5.
		III. (4) Nicotine only.	II. 3.4.
			III. No aortic lesions noted.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration (cont.)*

Author, year, country, reference	Number and type of animal	Procedure	Results
Wenzel et al., 1959, U.S.A. (*127*).	Rabbits	I. (12) Control untreated. II. (12) Control diet plus 1 percent cholesterol and 5 percent cottonseed oil added. III. (12) Control diet plus oral nicotine 2.28 mg./kg./day. IV. (12) Regimen II plus oral nicotine 2.28 mg./kg./day. V. (12) Regimen II plus oral nicotine 1.42 mg./kg./day. VI. (12) Regimen II plus oral nicotine 0.57 mg./kg./day.	General findings: Marked aortic pathologic involvement was noted in all cholesterol-treated groups; however, no difference was noted between Group II. and Groups IV., V., and VI. Cardiac histopathology: I. No change. II. Advanced atherosclerotic changes in the subendocardial vessels. III. Thickening and fibrosis of coronary artery small branches. IV.–VI. More severe changes with greater fatty metamorphosis and actual early myocardial necrosis, but no dose-dependent effects observed.
Thienes 1960, U.S.A. (*184*).	Newborn rats and mice.	Nicotine subcutaneously up to 5 mg./kg. twice daily by the end of 1 month. Animals autopsied at 1 year.	No arterial pathology noted. Medial degeneration seen more frequently in controls. Suggests that older animals be used.
Grosgogeat et al., 1965. France (*75*).	Male rabbits	I. (10) Nicotine subcutaneously 0.75 mg./day. (10) Controls—saline injected. Sacrificed at from 20–120 days. II. (27) Same as Group I. (27) Controls—saline injected. Sacrificed at 90 days. III. (66) Nicotine subcutaneously 0.3–1.5 mg./day. Sacrificed at 30 days. IV. (24) Nicotine subcutaneously 0.75 mg./day. (24) Controls—saline injected. One-half of each group ate cholesterol-enriched diet (0.5–1.0 percent cholesterol added). Sacrificed at 60 days.	Significant differences in aortic subendothelial fibrosis between control and experimental groups noted only in II and IV. In group IV, the nicotine-treated group showed more severe changes.

TABLE A23.—*Experiments concerning the atherogenic effect of nicotine administration (cont.)*

Author, year, country, reference	Number and type of animal	Procedure	Results
Hass et al., 1966, U.S.A. (*80*).	Male rabbits	*Nicotine* / *Diet* / *Vitamin D* I. (8) Control / Control / Control II. (7) Control / Cholesterol / Control III. (14) Nicotine / Control / Control IV. (15) Nicotine / Cholesterol / Control V. (9) Control / Cholesterol / Vitamin D VI. (14) Nicotine / Cholesterol / Vitamin D (Sacrificed at various times) Control—no treatment. Nicotine—subcutaneous injections in oil—increasing amounts 2 times per week. Vitamin D—subcutaneous injections up to 6–8 x 10^5 IU. Cholesterol—250–500 mg. cholesterol added per 100 g. diet.	I. Infrequent medial calcific disease without lipid localization. II. No medial calcific disease but frequent intimal atheroma formation. III. Rare calcific medial degeneration; no intimal atheromatous disease. IV. The largest number of atheromatous lesions. V. No medial calcific disease. VI. Consistent medial calcific disease.
Choi, 1967, Korea (*42*).	Albino rabbits	I. Nicotine 1–5 mg./kg./day intraperitoneally. Cholesterol 1 g./day (in varying combinations with controls). II. Nicotine alone. III. Cholesterol alone. (Sacrificed at 60 days)	I. Increasing nicotine dosages were associated with decreased atheroma formation (findings not statistically significant). II. Nicotine alone produced no atheroma formation but was associated with the presence of aortic medial calcification and endothelial hyperplasia. III. Cholesterol alone was associated with a definite increase in atheroma formation.
Stefanovich et al., 1969, U.S.A. (*178*).	Female albino rabbits.	I. (10) Diet supplemented with 2.0 percent cholesterol. Nicotine intramuscularly 2.78 mg./kg./day, 5/7 days. II. (10) Cholesterol only. III. (10) Nicotine only. IV. (10) Control.	*Percent of aortic surface involved with atherosclerosis* I. 9.4 II. 5.7 III. 0.1 IV. . .	In both stock and cholesterol-fed animals, nicotine was also noted to increase aortic triglyceride content and to decrease aortic free cholesterol content.

TABLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids*
(Human Studies)

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Page et al., 1959, U.S.A. (*147*).	13 male and 7 female laboratory workers 17–51 years of age.	2 nonfiltered cigarettes in 10 minutes and blood levels measured over 30-minute period.		No change.		*Serum lipoproteins* No change (10 subjects).	
Kershbaum et al., 1961, U.S.A. (*104*).	31 male patients or staff 16–72 years of age, 7 normals, 7 CHD, 17 other medical diagnoses.	I. 17 subjects smoked 2 non-filter cigarettes in 10 minutes. II. 9 controls. III. 5 subjects smoked 6 cigarettes in 40 minutes.	*Mean rise* I. 351 μEq./L. II. 9.8 μEq./L. III. 272–2,304 μEq./L.	No change.	No change.		The authors consider the increase among controls to be due to fasting.
Kershbaum et al., 1962, U.S.A. (*103*).	I. 17 male patients with healed myocardial infarctions. II. 16 non-CHD patients. III. 10 normals. IV. 13 normals.	I., II., III., 2 non-filter cigarettes in 10 minutes. IV. No smoking.	*Mean rise* I. 858 μEq./L. II. 320 μEq./L. III. 292 μEq./L. IV. 20 μEq./L.				No difference found between results following inhalation or noninhalation. Statistically significant difference found between increases in Groups II and III and Group I.

TABLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids (cont.)*

(Human Studies)

[SM — Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Kershbaum et al., 1963, U.S.A. (*109*).	11 normal patients.	9 standard cigarettes in 3 hours. Samples at 10, 20, and 40 minutes of smoking period.	Definite increase at start of smoking period.			3 patients with trimethaphan camphorsulfonate (Arfonad) pretreatment and 8 formerly adrenalectomized patients showed either minimal or no elevation.	Both free and total urinary catecholamines increased with smoking and the author considers them as mediators of the FFA increase.
Konttinen and Rajasalmi, 1963, Finland (*120*).	40 healthy moderate smokers 19–20 years of age.	Fed at fat meal and then 20 were allowed to smoke cigarettes of known-nicotine content over 6 hour period (approximately 23 cigarettes consumed).	NS—definite increase at 6 hours. SM—definite increase at 6 hours.	No change in either group.	NS—definite increase at 2 hours. SM—slight increase at 2 hours.		
Kedra et al., 1965, Poland (*101*).	37 male and 5 female medical students 22–23 years of age.	3 cigarettes smoked in rapid succession and samples taken at 10 and 30 minutes.	No change.	No change.		Beta-lipoproteins definite increase.	

TABLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids (cont.)*

(Human Studies)

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Frankl et al., 1966, U.S.A. (*66*).	5 male and 1 female healthy smokers 24-29 years of age.	2 standard cigarettes inhaled in 10 minutes.	No change.				Subjects were in nonfasting, nonbasal state.
Kershbaum et al., 1966, U.S.A. (*106*).	43 normal male heavy cigarette or cigar smokers, 21 46 years of age.	I. Terminal segment of cigar in 20 minutes—15 subjects. II. 3 cigarettes in 20 minutes 15 subjects (including 6 from group I). III. Cigarette inhalation or noninhalation 6 subjects.	I. Indefinite increase. II. Definite increase. III. Increase with inhalation greater than with non-inhalation in every subject.				Cigar smoking in 11 subjects showed an intermediate increase in the excretion of urinary catecholamines as compared to that with cigarette smoking.
Klensch, 1966, Germany (*118*).	56 observations on student smokers 20–24 years of age.	1 standard cigarette in 4 minutes. FFA measured at 16–25 minutes.	Definite increase.				Indefinite increase in venous epinephrine levels.